EXHIBIT 2

UNITED STATES DISTRICT COURT
SOUTHISN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO** **Margaret Acosta, et al. v. Ethicon, Inc., et al** **Case No. 2:17-cv-02702**	**Master File No. 2:12-MD-02327** **MDL No. 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE** **WAVE 12**

RULE 26 EXPERT REPORT OF DR. NIALL GALLOWAY

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. The opinions, which are held to a reasonable degree of medical certainty and expressed are as follows:

I. QUALIFICATIONS

I am an Associate Professor of Surgery (Urology) at the Emory University School of Medicine in Atlanta, Georgia. I obtained a M.B., Ch.B. from the University of Aberdeen Medical School in 1974 and went on to Edinburgh, Scotland for internship. I was awarded Fellowship of the Royal College of Surgeons of England in 1979 and was later awarded Fellowship of the Royal College of Surgeons of Edinburgh. I completed my residency in surgery in 1980 at Royal United Hospital in Bath, England.

I was appointed Lecturer in Surgery/Urology at the University of Edinburgh in 1982. At that time, I was able to initiate collaboration between the Urology and Gynecology specialties, which led to the creation of the first multidiscipline Continence Clinic in Scotland. I was appointed Senior Registrar in 1984 at the University Hospital of Wales in Cardiff. In 1986, I was invited to Duke University as a Research Fellow and was later appointed to the faculty as visiting professor. I was invited to join the faculty of Emory University School of Medicine in Atlanta in 1988. In 1992, I co-founded the Emory Continence Center, where I presently serve as Medical Director. The Continence Center is staffed by Urology, Gynecology and Gastroenterology physicians, as well as specialty trained continence nurses. The center provides all aspects of comprehensive assessment and treatments for pelvic floor dysfunction including incontinence, prolapse, bowel problems, and pelvic pain.

I was elected to the Atlanta Urological Association in 1990, the Southeastern Section of

the American Urological Association AUA in 1993, and by invitation to the National Urological Forum in 1994. From 2007 to 2008, I served on the Medical Executive Committee of the Georgia Urological Association. I have recently stepped down from the position of Chairman of the Board of Directors for the National Association for Continence, after serving two consecutive terms. I have been a member of the editorial board for the European Association of Urology since 2011. I am an author of many book chapters, abstracts, and peer reviewed journal articles and have given presentations regarding pelvic floor disorders, including pelvic organ prolapse (POP) and stress urinary incontinence (SUI). I have recently published a new book titled "Seeking Symmetry: Finding Patterns in Human Health".

My experience, education, and training are more fully summarized in my curriculum vitae, attached to this report as Exhibit A. A list of the Materials I have reviewed and relied on in this case is attached as Exhibit B.

II. INTRODUCTION

Over the past several years, more and more of my surgical practice consists of handling complications resulting from the placement of synthetic mesh in the vagina for POP and SUI. I see several new patients every month with mesh-related complications. Synthetic mesh can take a trivial condition and raise a host of aggravating problems that interfere with activities of normal life. Surgeons and physicians saw these problems soon after these products were introduced. The most common complaints are pain and dyspareunia from banding, scarring, shrinkage, and contraction of the mesh.

In the introduction of trans-vaginally-placed mesh devices into the medical marketplace for the treatment of SUI, a basic principle of medicine was violated; that is, "Do No Harm." These products were introduced into the marketplace despite red flag alerts from the hernia experience and literature, the known uniqueness of the vaginal environment, and early adverse event reports. As a result, a public health crisis has been created. Women have been forced to deal with serious and unanticipated complications and doctors have been confronted with conditions that are difficult, and sometimes impossible, to treat. All of this was predictable.

The opinions expressed in this report are based on my experience treating women with mesh complications and surgically removing mesh and the medical and scientific literature. All my opinions have been made to a reasonable degree of medical certainty.

III. DISCUSSION

The extrapolation of the placement of mesh in other parts of the body (e.g., the abdominal wall) to the vagina was an erroneous idea. The vagina is a unique environment. Although the vagina can be forgiving (as in accommodating a vaginal birth and the remarkable healing afterwards), it can also be as hostile as any area in the human body. The vagina is also extremely variable from one individual to the next and over time. Synthetic mesh devices failed to take into consideration biological and anatomical differences of the vagina.

1. A permanent synthetic mesh device designed to be placed in a contaminated environment (i.e., vagina) contradicts basic surgical principles.

The vagina is populated and colonized with numerous bacteria and yeast and is located immediately adjacent to the bowel and anus.

The vagina is the only area of the body in which polypropylene mesh is placed in a bacteria laden surgical field. In fact, the placement of polypropylene mesh is actually contraindicated in this setting. Choi reported on the outcomes of 33,832 cases of ventral hernia repair with mesh. The authors of this study concluded, "there is a significant increase in risk of postoperative occurrences following VHRs [ventral hernia repairs] using mesh in clean-contaminated and contaminated cases relative to clean cases." The study recommended avoiding the use of mesh in any level of contamination.[1]

Culligan and others have shown that bacterial colonization exists even after attempts to sterilize the vagina in preparation for surgery. Even following standard surgical scrub with providone-iodine and pre-operative antibiotics, the majority of women (52%) had positive cultures at 30 minutes. Bacteria found in baseline (preoperative) vaginal cultures included anaerobic pathogens (45%), staphylococcus aureus (16%), alpha-hemolytic streptococcus (23%), E. coli (42%), klebsiella pneumonia (13%), and Group B streptococci (13%).[2]

Synthetic mesh materials are prone to infections and "notoriously resistant to antibiotics and host defenses, and to persist until the biomaterial is removed."[3] In a prospective study of 64 consecutive patients undergoing vaginal implantation of a lightweight, collagen-coated monofilament polypropylene mesh, Vollebregt, et al. showed that 96 % of the mesh arms were colonized by different types of bacteria.[4] The bacteriological analysis of 16 meshes removed because of complications following the surgical management of urinary incontinence or POP showed multimicrobial infection in 31% of cases, including P. mirabilis (in 25%), E. coli, Staphylococcus, Streptococcus and Enterococcus [8]. Bacterial contamination was found in all meshes, even in a case of repeat surgery for mesh shrinkage with no erosion. Bacterial density was low (<103 CFU/mL) in 43% of cases but in others reached 10^5 CFU/mL.[5]

[1] Choi, J. J., Palaniappa, N. C., Dallas, K. B., Rudich, T. B., Colon, M. J., & Divino, C. M. (2012). Use of mesh during ventral hernia repair in clean-contaminated and contaminated cases: outcomes of 33,832 cases. Ann Surg, 255(1), 176-180. doi: 10.1097/SLA.0b013e31822518e6

[2] Culligan, P., Heit, M., Blackwell, L., Murphy, M., Graham, C. A., & Snyder, J. (2003). Bacterial colony counts during vaginal surgery. Infect Dis Obstet Gynecol, 11(3), 161-165. doi: 10.1080/10647440300025515

[3] de Tayrac, R., & Letouzey, V. (2011). Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery. Int Urogynecol J, 22(7), 775-780. doi: 10.1007/s00192-011-1405-4

[4] Vollebregt, A., Troelstra, A., & van der Vaart, C. H. (2009). Bacterial colonisation of collagen-coated polypropylene vaginal mesh: are additional intraoperative sterility procedures useful? Int Urogynecol J Pelvic Floor Dysfunct, 20(11), 1345-1351. doi: 10.1007/s00192-009-0951-5

[5] Boulanger, L., Boukerrou, M., Rubod, C., Collinet, P., Fruchard, A., Courcol, R. J., & Cosson, M. (2008). Bacteriological analysis of meshes removed for complications after surgical management of urinary incontinence or pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct, 19(6), 827-831. doi: 10.1007/s00192-007-0537

Lactobacili dominate the normal bacteria seen in the vagina and routinely produce hydrogen peroxide and lactic acid. "Their toxic and inhibitory effect against the overgrowth of pathogens in the vagina is documented by in vitro studies."[6] This issue becomes important since peroxides are implicated in the oxidation and degradation of polypropylene in the human body.

Infection, even subclinical, has been linked with misbehaving mesh and mesh complications, including chronic infection and abscess, wound separation, erosion, fistulae, shrinkage, chronic inflammation, degradation, and functional bladder problems. In a study by Wang, bacterial colonization was also linked to de novo urge symptoms after placement of mesh. In that study, 83% of patients with urge symptoms had bacteria identified in the excised tissue, compared to 5% in controls.[7]

The difference in the abdomen and vagina was demonstrated as early as 2000. Visco et al., reporting on their experience with sacral colpopexy, noted that "the rate of mesh erosion is higher and the time to mesh erosion is shorter with combined vaginal-abdominal sacral colpoperineopexy with vaginal suture and vaginal mesh placement in comparison with abdominal sacral colpopexy." The erosion rate with traditional sacral colpopexy was noted to be 4.5% whereas the erosion rate when mesh was placed vaginally was 40%. As a result, the investigators discontinued the practice of attaching vaginal mesh directly to the perineal body and concluded that "mesh erosions may be the only clinical manifestations of a bacterial contamination."[8]

It was foreseeable that placing mesh in a contaminated environment would create problems, e.g. de novo infection, abscess, erosion, and pain.

In my opinion, inserting polypropylene mesh (known to be problematic when placed in a contaminated field) in the vagina (known to contain bacteria, known to be close to the anus, and known to be incapable of sterilization) represents a serious flaw in the design of Ethicon's mesh devices.

[6] Mijac, V. D., Dukic, S. V., Opavski, N. Z., Dukic, M. K., & Ranin, L. T. (2006). Hydrogen peroxide producing lactobacilli in women with vaginal infections. Eur J Obstet Gynecol Reprod Biol, 129(1), 69-76. doi: 10.1016/j.ejogrb.2005.11.036

[7] Wang, A. C., Lee, L. Y., Lin, C. T., & Chen, J. R. (2004). A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: a prospective case-controlled pilot study. Am J Obstet Gynecol, 191(6), 1868-1874. doi: 10.1016/j.ajog.2004.09.017

[8] Visco, A. G., Weidner, A. C., Barber, M. D., Myers, E. R., Cundiff, G. W., Bump, R. C., & Addison, W. A. (2001). Vaginal mesh erosion after abdominal sacral colpopexy. Am J Obstet Gynecol, 184(3), 297-302. doi: 10.1067/mob.2001.109654

2. Polypropylene becomes rigid when placed in the vagina - an organ that needs to remain flexible and compliant to function. This phenomenon leads to complications not seen with traditional pelvic surgery.

The pelvic floor is a dynamic trampoline of resilient muscles and connective tissue structures. It needs to be supple, flexible, and springy. The muscles and loose connective tissue are critical for normal pelvic support. They must contract to maintain pelvic support for continence. They must relax to permit voluntary urination and to initiate the act of defecation. In the female, the pelvic floor must relax and lengthen enormously to allow the passage of a full-term fetus during childbirth, yet it must contract again after delivery to permit all of the normal functions to be maintained. It must accommodate movement and forces associated with activities of daily living, such as coughing, walking, exercise, bladder filling, defecation, and sexual relations. Scar plate and mesh stiffness are incompatible with the natural functioning of the vagina.

Mesh embrittlement, resulting in restriction of movement of the abdominal wall, has been recognized in hernia repairs for some time. In 2001, Junge and Klinge used fresh cadavers to test the elasticity of abdominal wall mesh. The authors reported that the implantation of mesh "leads to considerable restriction of abdominal wall mobility in up to 25% of cases. Rigidity and discomfort, especially at the edge of the mesh, are frequent reported complaints." Junge stated that tensile strength and flexibility must be taken into account in the "complex interactions of the anatomic structures" where the mesh is placed. Inadequate pore size and geometry result in increased shrinkage and scar reaction. Junge found most of the meshes he tested to be "inappropriately stiff" and these turned into a "hard sheet in the post-implantation period."[9]

"The mechanism of action of a permanent prosthetic mesh is to incite an intense fibroplastic foreign body response, resulting in the development of a strong scar plate interface. Although this may provide a strong and durable repair, the chronic inflammatory response to the mesh may also lead to chronic pain in some patients, a sensation of being able to feel the mesh, and stiffness of the abdominal wall with loss of

compliance."[10] In addition to stiffness from scarring and fibrosis, degradation of the polymer itself results in stiffening.[11]

[9] Junge, K., Rosch, R., Klinge, U., Schwab, R., Peiper, C., Binnebosel, M., . . . Schumpelick, V. (2006). Risk factors related to recurrence in inguinal hernia repair: a retrospective analysis. Hernia, 10(4), 309-315. doi: 10.1007/s10029-006-0096-0

[10] Bellows, C. F., Shadduck, P. P., Helton, W. S., & Fitzgibbons, R. J. (2011). The design of an industry- sponsored randomized controlled trial to compare synthetic mesh versus biologic mesh for inguinal hernia repair. Hernia, 15:325-332. doi: 10.1007/s10029-010-0773-x

[11] Costello CR, Bachman SL, Ramshaw BJ, Grant SA. Materials characterization of explanted polypropylene hernia meshes. Journal of biomedical materials research Part B, Applied biomaterials. 2007;83(1):44-9; C.R. Costello SLB, S.A. Grant, D.S. Cleveland, T.S. Loy and B.J. Ramshaw. Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants From a Single Patient. Surgical Innovation. 2007;14(3):168-76.; Fayolle B, Audouin L, Verdu J. Oxidation induced embrittlement in polypropylene - a tensile testing study. Polymer Degradation and Stability. 2000;70(2000):333-40; Fayolle B, Audouin L, Verdu J. Initial steps and embrittlement in the thermal oxidation of stabilised polypropylene films. Polymer Degradation and Stability. 2002;75:123-9; Fayolle B, Audouin L, George GA, Verdu J. Macroscopic heterogeneity in stabilized polypropylene thermal oxidation. Polymer Degradation and Stability. 2002;77:515-22; Liebert TC, Chartoff RP, Cosgrove SL, McCuskey RS. Subcutaneous implants of polypropylene filaments. Journal of biomedical materials research. 1976;10(6):939-51; Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Seminars in immunology. 2008;20(2):86-100.

The loss of vaginal compliance and function from hardened mesh is something I commonly see in my practice. Mesh, when surgically removed, does not look or feel anything like it does in the package.

In my opinion, placing polypropylene mesh (known to become rigid and restrictive of motion) in the vagina (known to require flexibility and compliance for proper function) represents a serious flaw in the design of Ethicon's vaginal mesh devices.

3. Degradation, chronic inflammation, and possible toxicity create unknown long-term effects in a woman's vagina.

A chronic inflammatory and foreign body reaction to transvaginally placed mesh occurs in all patients.[12]Additionally, Polypropylene was known to degrade in the human body as early as 1986[13]. This was reported again by Coda and Bendavid in 2003[14] and frequently since that time. Degradation and mesh surface changes contribute to the inflammatory response and scar plate formation by harboring bacteria, releasing toxins,

and creating a jagged surface. In a 2007 study of explanted polypropylene hernia mesh, Costello et al. reported cracks, surface roughness, and peeling – all indicative of degradation. The authors also recognized reduced compliance. "These findings correspond to increased abdominal wall stiffness and patient complaints of pain and restricted mobility. During the implantation period, the surface of the explanted materials stimulated the foreign body response that, in turn, produced oxidants such as hydrogen peroxide and hypochlorous acid."[15]

Clave confirmed degradation in transvaginal mesh explants in 2010. Clave questioned "the prevailing understanding of PP as inert" based on his examination of 100 explants. In Clave's work, "not all types of PP implants degraded equally. The PP implants degraded more in the presence of an acute infection or chronic inflammation." Clave considered several hypotheses for this degradation, including large detachments and hematomas causing the massive accumulation of blood-derived fatty acids, the diffusion of organic molecules into the polymer, and radical oxidation due to the septic environment that accompanies acute infections and chronic inflammation.[16] Several recent studies have confirmed degradation in explanted vaginal mesh.[17]

In my opinion, placing a material that degrades, releases potentially toxic chemicals, and creates a chronic inflammatory response, is a flaw in the design of Ethicon's vaginal mesh devices.

[12] Iakovlev V., C. E., Steege J (2014). "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8(9).

[13] Jongebloed, W. L., & Worst, J. F. Degradation of polypropylene in the human eye: a SEM-study. Documenta Ophthalmologica. Advances In Ophthalmology,1986: 64(1), 143-152.

[14] Coda, A., Bendavid, R., Botto-Micca, F., Bossotti, M., & Bona, A (2003). Structural alterations of prosthetic meshes in humans. Hernia: The Journal Of Hernias And Abdominal Wall Surgery, 7(1), 29-34.

[15] Costello, C. R., Bachman, S. L., Grant, S. A., Cleveland, D. S., Loy, T. S., & Ramshaw, B. J. (2007). Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov, 14(3), 168-176. doi: 10.1177/1553350607306356[16] Clave, A., Yahi, H., Hammou, J. C., Montanari, S., Gounon, P., & Clave, H. (2010). Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J, 21(3), 261-270. doi: 10.1007/s00192-009-1021-8

[17] Iakovlev V. MG, Blaivas J. Pathological Findings of Transvaginal Polypropylene

Slings Explanted for Late Complications: Mesh is Not Inert [Abstract]. International Continence Society Meeting Annual Meeting. 2014; Iakovlev V., C. E., Steege J (2014). "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8(9); Iakovlev, V., Guelcher, S., Bendavid, R. (2014). "In vivo degradation of surgical polypropylene meshes: A finding overlooked for decades." Virchows Arch Suppl 1: S35; Tzartzeva K, L. D., Baniasadi M, Minary-Jolandan M, Zimmern P (2014). "In-Depth Nan-Investigation of Vaginal Mesh and Tape Fiber Explants in Women [Abstract]." ICS 366.

[18] Klinge, U., Klosterhalfen, B., Muller, M., Ottinger, A. P., & Schumpelick, V. (1998). Shrinking of polypropylene mesh in vivo: an experimental study in dogs. Eur J Surg, 164(12), 965-969. doi: 10.1080/110241598750005156

4. Ethicon's transvaginal mesh devices demonstrate a variable and unpredictable rate of shrinkage and retraction, rendering performance that is unreliable at best.

In 1998, Klinge and Klosterhalfen reported a 30-50% shrinkage rate with polypropylene mesh.[18] In practice, surgeons knew for even longer that a mesh piece must be cut significantly larger than the defect to avoid failure at the edges, indicating concern for shrinkage and puckering. Tunn confirmed shrinkage using ultrasound evaluation of transvaginal mesh in 2007.[19] Jacquetin and Cosson linked mesh retraction with vaginal tenderness, painful intercourse, pain, sometimes permanent, and possibly urinary dysfunction.[20]

Because of shrinkage and retraction, there is no way to place synthetic mesh in a "tension-free" manner and it is impossible to know how much tension will eventually result. The degree of shrinkage is unpredictable and varies from one individual to the next – some women are high responders and others are low responders to biomaterials, including polypropylene. The amount of shrinkage has also been shown to vary based on the location in which it is placed (between the peritoneum and muscle or above the fascia).[21] Shrinkage is magnified with infection, even subclinical contamination, which has been found to occur in almost all transvaginally placed meshes.[22] Letouzey showed polypropylene mesh contraction to be progressive, demonstrating a linear evolution with time. Ultrasound reconstruction "showed a mean contraction of 30%, 65%, 85% at a mean follow up of 3 years (n 5 12), 6 years (n 5 16), 8 years (n 5 12) respectively."[23]

Chronic pelvic pain is the most common clinical symptom associated with mesh shrinkage. "The concurrent processes of tissue in growth and mesh shrinkage may cause significant pain, particularly in patients who undergo trocar-guided mesh placement. Adherence of the mesh arms in the lateral pelvic wall is a point against which tension increases during the processes of tissue in growth and mesh shrinkage." Other complications related to shrinkage and not warned about by Bard include sexual

impairment, loss of vaginal function due to narrowing/shortening, functional bladder and bowel symptoms, and need for multiple, difficult corrective procedures.[24] Chronic pain from mesh distortion and shrinkage is something I commonly see in my practice.

In a study by Margulies, "[t]he repercussions of mesh shrinkage in the vagina vs the abdominal wall can be severe and functionally devastating. Normal urinary, sexual, and defecatory functions require a vagina that is compliant and whose walls can easily and painlessly change conformation. With excessive stiffness of the vaginal walls secondary to mesh that has undergone shrinkage, it is possible that dyspareunia, defecatory, and urinary dysfunction could result." The conditions described in this article are something I commonly see in my practice.[25]

An example of a clinical study exhibiting the defects in armed transvaginal mesh was published by Feiner and Maher in 2010, based on a series of patients seen in 2007- 2008. This paper described the "substantial morbidity" associated with "vaginal mesh contraction". "Clinical presentation included severe vaginal pain aggravated by movement (17 of 17), dyspareunia in all sexually active women (14 of 14), and focal tenderness over contracted portions of the mesh on vaginal examination (17 of 17), commonly involving the lateral fixation arms. Mesh erosion (9 of 17), vaginal tightness (7 of 17), and shortening (5 of 17) were frequently present." This paper set out to describe the clinical implications of the in vivo shrinkage of polypropylene mesh up to 50% if its original size that had been previously described both in animal studies and women.[26] Vaginal contraction from mesh procedures is something I commonly see in my practice.

[19] Tunn, R., Picot, A., Marschke, J., & Gauruder-Burmester, A. (2007). Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol, 29(4), 449-452. doi:10.1002/uog.3962

[20] Jacquetin, B., & Cosson, M. (2009). Complications of vaginal mesh: our experience. Int Urogynecol J Pel Floor Dysfunct, 20(8), 893-896. doi:10.1007/s00192-009-0926-6

[21] Garcia-Urena, M. A., Vega Ruiz, V., Diaz Godoy, A., Baez Perea, J. M., Marin Gomez, L. M., Carnero Hernandez, F. J., & Velasco Garcia, M. A. (2007). Differences in polypropylene shrinkage depending on mesh position in an experimental study. Am J Surg, 193(4), 538-542. doi: 10.1016/j.amjsurg.2006.06.045.

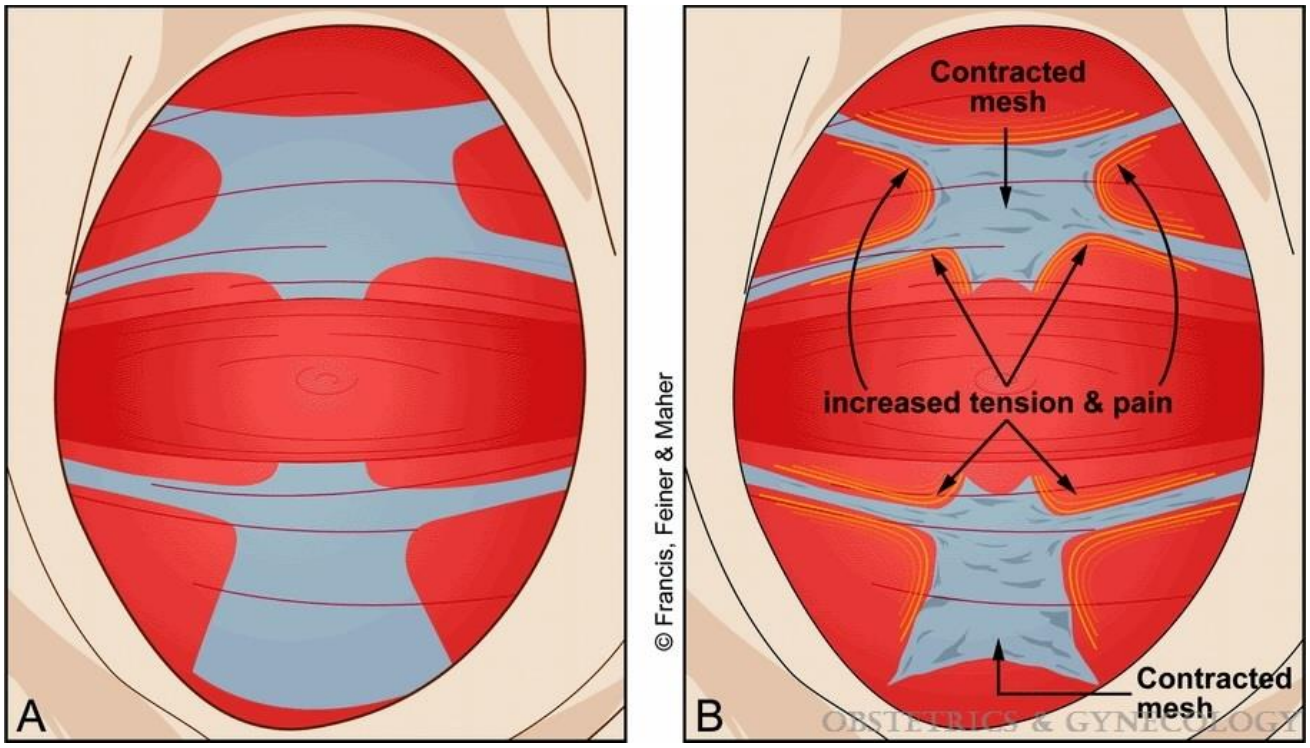
[22] Mamy, L., Letouzey, V., Lavigne, J. P., Garric, X., Gondry, J., Mares, P., & de Tayrac, R. (2011). Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J, 22(1), 47-52. doi: 10.1007/s00192-010-1245-7

[23] Letouzey, V., Huberlant, S., Lavigne, J., Mares, P., Garric, X. & De Tayrac, R. (2012). Is polypropylene mesh coated with antibiotics is efficient to prevent mesh infection and contraction in an animal infectious model? [Abstract]. 37th Annual Meeting of the International Urogynecological Association, 193.

[24] Rogo-Gupta, L., & Raz, S. (2013). Pain Complications of Mesh Surgery. In H. B. Goldman (Ed.), Complications of Female Incontinence and Pelvic Reconstructive Surgery (pp. 87-105): Humana Press.

[25] Margulies, R. U., Lewicky-Gaupp, C., Fenner, D. E., McGuire, E. J., Clemens, J. Q., & Delancey, J. O. (2008). Complications requiring reoperation following vaginal mesh kit procedures for prolapse. Am J Obstet Gynecol, 199(6), 678 e671-674. doi: 10.1016/j.ajog.2008.07.049

[26] Feiner, B., & Maher, C. (2010). Vaginal mesh contraction: definition, clinical presentation, and management. Obstet Gynecol, 115(2 Pt 1), 325-330. doi: 10.1097/AOG.0b013e3181cbca4d



Feiner, Benjamin; Maher, Christopher: Obstetrics & Gynecology. 115(2, Part 1): 325-330, February 2010.

In my opinion, using a material that shrinks and retracts significantly, but in a variable

and asymmetric fashion, is a flaw in design.

5. Ethicon's transvaginal mesh devices damage and entrap nerves, sometimes resulting in chronic and permanent pain syndromes that are refractory to treatment.

Unlike routine postoperative pain that is typically self-limiting, mesh-related pain is often atypical in character, onset, duration, and location. Neuropathic pain associated with mesh is something I see commonly in my practice and can be very difficult to treat.

Nerve injuries occur commonly with transvaginally placed mesh. The trocars, blindly placed, traverse through tissue densely innervated with large nerves and smaller nerve branches. Nerves can be traumatized during the procedure itself. Postoperative nerve injuries have been reported to occur at a rate of 9.4% with transobturator slings.[27]

Nerve damage can also result from nerve inflammation and nerve entrapment resulting from the chronic inflammatory response and fibrosis surrounding the mesh. The nerves most commonly involved with a transobturator sling are the intermediate femoral cutaneous, posterior cutaneous, pudendal, perineal, inferior anal, and the obturator nerves. The ilioinguinal and iliohypogastric nerves are more commonly involved with the retropubic approach.

In a 2005 Klosterhalfen post-retrieval study of hernia mesh, most explants from all the patients with chronic pain in their medical history indicate nerve fibers and

[27] Richter, H. E., Albo, M. E., Zyczynski, H. M., Kenton, K., Norton, P. A., Sirls, L.T., Litman, H. J. (2010). Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med, 362(22), 2066-2076. doi: 10.1056/NEJMoa0912658

fascicles in the interface of the mesh. Klosterhalfen further stated that "clinical trials report high percentages of patients with chronic pain after hernia repair, including mesh repair. In contrast to neuropathy-related complaints after intraoperative damage of nerve fibers with pain immediately after surgery, the onset of chronic pain as a consequence of the FBR [foreign body reaction] is typically more than 1 year after hernia repair. In the postretrieval study, most explants from all the patients with chronic pain in their medical history, indicate nerve fibers and fascicles in the interface of the mesh."[28]

Drs. Iakovlev and Ben-David recently published an article in the peer-reviewed literature titled, "Mesh-Related SIN Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain". This paper describes nerve ingrowth with hernia mesh and reports a new mesh-related pain disorder characterized by its slow onset, its progressive and unrelenting nature, and its unresponsiveness to treatment including mesh removal.[29] Drs. Iakovlev and Blaivas have also published their findings of nerve damage in vaginal mesh – occurring with a much

greater density than the abdominal wall. These published reports of explanted mesh pathology also describe chronic inflammation, scarring and fibrosis, deformation, and degradation. 30

Histological findings in transvaginal mesh:

Rogo-Gupta stressed the importance of a thorough understanding of pelvic anatomy in evaluating complex mesh pain.[31] Mesh can become incorporated into muscles,

[28] Klosterhalfen, B., Junge, K., & Klinge, U. (2005). The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices, 2(1), 103-117. doi:10.1586/17434440.2.1.103

[29] Bendavid, R., Lou, W., Koch, A., Iakovlev, V. (2014). "Mesh-Related SIN Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain." International Journal of Clinical Medicine 5: 799-810.

[30] Iakovlev V., M. G., Blaivas J. (2014). "Pathological Findings of Transvaginal Polypropylene Slings Explanted for Late Complications: Mesh is Not Inert [Abstract]." International Continence Society Meeting Annual Meeting.

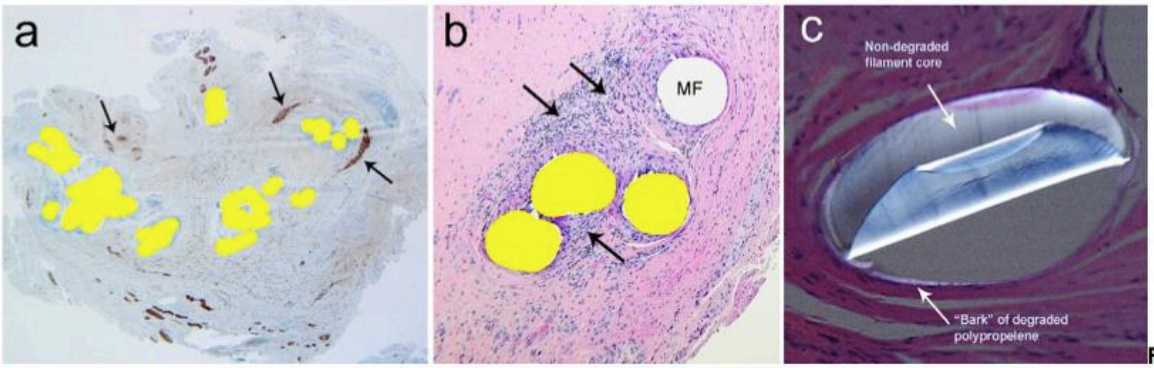


Figure 1. a: Nerve ingrowth. 2.5x objective, S100 stain to highlight nerves (dark brown, some nerves pointed by arrows). Mesh filaments are filled yellow for demonstration. **b:** Foreign body and non-specific chronic inflammation. H&E stain, 20x objective, three filaments filled yellow, one left unfilled (MF), inflammation pointed by arrows. **c:** Polypropylene degradation. 40x objective, partially polarized light. The bark of degraded polypropylene surrounds the central core (in the picture the core detached and folded). Both, the core and the bark show the same polarizing properties (brightly lit). The bark absorbs histological dyes due to it porosity and stains purple while the core remains clear (MF filament left clear in panel "b").

10

resulting in fibrosis, restriction and pain with movement. Muscular injury with armed mesh may cause severe pain with walking or joint movement. Patients who undergo posterior compartment mesh repair with trocar-guided lateral mesh arms may experience pain in the levator muscles or gluteus maximus. Gluteus maximus innervation is provided by the inferior gluteal nerve (S1). Patients may present with pain exacerbated by sitting, external hip rotation, and hip extension. Injury to the external anal sphincter muscles may cause pain or defecatory dysfunction including constipation or incontinence of flatus or

stool. Intraoperative nerve damage presents immediately following the procedure. Sharp pain in a specific nerve distribution presenting in the immediate postoperative period suggests intraoperative nerve damage and should be treated.

"Nerve pain that presents in the postoperative period and persists into the delayed postoperative period should be considered an example of mesh pain and trigger evaluation for other etiologies as well. This includes nerve entrapment and the pelvic organ cross-talk or sensitization. Posterior compartment repair may cause injury to the lumbosacral plexus, sciatic nerve, or pudendal nerve."[32]

Chronic mesh pain syndrome (CMPS) is reported in the medical literature and refers to a complex condition that develops in some patients with pain following mesh reconstruction. This pain persists beyond the routine postoperative period and is characterized by its intensity. It is also refractory to medical and surgical treatment. Regional and systemic symptoms develop as a result of nerve up-regulation, cross-talk and central sensitization. CMPS is a pathologic condition caused by the transformation of local vaginal pain into a multiorgan systemic process.[33]

The potential for serious pain conditions resulting from the transvaginal mesh should have been apparent from the experience of hernia mesh in the abdominal wall and elsewhere in the body. Chronic pain is the most serious long-term complication that can occur after repair of groin hernia. The incidence of chronic pain after herniorrhaphy has been reported to be 30% or even higher. The complaint of chronic pain after inguinal hernia repair continues for months or even years. The development of chronic pain has been attributed to several mechanisms, including damage to sensory nerves and mesh inguinodynia.

In my opinion a medical device that injures and entraps nerves and muscle, sometimes resulting in chronic, severe, and intractable pain conditions, is flawed.

[31] Rogo-Gupta (2013). [32] Rogo-Gupta (2013). [33] Rogo-Gupta (2013).

6. Because of the unique design of the pelvic organ system, Ethicon's transvaginal mesh devices can result in bowel problems, bladder problems, and sexual dysfunction.

The vagina is a dynamic organ that must respond to motion and dynamic changes in adjacent organs (bowel and bladder) and with sexual relations. The space is shared and confined between all the pelvic organs and they need to move in relation to one another.

If nerves and muscles are present and are functioning properly, the pelvic floor is a versatile dynamic structure with the possibility of fine regulation of muscle activity. The innervation of the lower urinary tract is complex and includes sensory and motor functions as well as somatic and autonomic systems. The urethra is like the mouth or the larynx, innervated by the right and left. Motor neurons and muscle fibers are arranged in independent functional units called motor units, and a limited number of motor units are

responsible for muscle control. The greater the number of motor nerurons to the urinary sphincter, the greater the number of motor units, and the more versatile the range of possible muscle activity. Conversely, the lesser the number of motor neurons, the less versatile or more clumsy the possible range of sphincter activity. Patients with neurologic deficits in the pelvis may demonstrate irritative bladder symptoms and variable degrees of voiding difficulty and dysfunction.

Anorectal and bowel problems, likewise, are mediated by a complex arrangement of nerves and muscles in the pelvis. The normal act of defecation is easy and complete. The bowel should function with the effortless displacement of the stool from the lower bowel. After normal defecation, the sigmoid colon and rectum are empty and the stool is gone. If there is impairment of the nerves and muscles of the lower bowel, the function is more likely to be incomplete, and instead of the train leaving the station, only one or two cars might leave, but the bulk of the train continues to stand. The rectum and sigmoid colon remain loaded with stool most of the time. Constipation, diarrhea, irritable bowel symptoms, and pain can be associated with the loss of versatile sphincter and pelvic floor function.

Shared nerves means shared behaviors, and Kaplan et al. described this phenomenon as "crosstalk", the functional relationship between bladder and bowel. "The connection between bladder and bowel function is apparent in several clinical disorders, including chronic pelvic pain syndromes, urinary and faecal incontinence, organic diseases involving the colon, functional bowel disorders and OAB."[34]

In my opinion, a device designed for treatment of SUI or POP that invites widespread bladder, bowel and sexual dysfunction is flawed.

[34] Kaplan, S. A., Dmochowski, R., Cash, B. D., Kopp, Z. S., Berriman, S. J., & Khullar, V. (2013). Systematic review of the relationship between bladder and bowel function: implications for patient management. Int J Clin Pract, 67(3), 205-216. doi: 10.1111/ijcp.12028

7. A permanent device that cannot be removed when complications dictate is unacceptable.

The medical literature contains numerous reports describing the difficulties and less than satisfactory outcomes associated with mesh removal. Those of us who are performing these surgeries on a regular basis know all too well the challenges of explant surgery. Putting mesh in is relatively easy. Taking it out is another matter. These surgeries are time-consuming, complicated, and risky for the patient. We never know what we will encounter until we get to the operating room. The anatomy is often distorted and healthy tissue often has to be removed along with the mesh. In many instances, it is impossible to remove the entire device. We are always concerned about the possibility of doing more harm than good. This is an entirely different situation from the treatment of any other surgical complication.

Rogo-Gupta described the technically challenging removal of armed mesh. "To successfully remove armed mesh segments in their entirety, the obturator membrane must be perforated and dissection carried out laterally. Additional incisions in the thighs may be required to adequately free the arms from the surrounding soft tissues. We suggest preoperatively marking the lateral puncture sites to facilitate intraoperative dissection. If the lateral incisions cannot be identified by patient symptoms or scarring, gentle traction on the medial portion of the mesh arms may be used as a guide. The mesh should be followed from skin incision to the intersection of the adductor muscles and dissected free in a circumferential fashion. Muscle fibers often must be dissected when mesh has become incorporated into the surrounding fibers. Large defects in the vaginal wall may occur with mesh removal and surgeons ought to be prepared to utilize rotational vaginal flaps, labial flaps, or skip flaps for reconstruction. Following complete healing and resolution of other symptoms such as pain, infection, bleeding, urinary or defecatory dysfunction, evaluation for additional surgery for persistent incontinence or prolapse can begin if clinically indicated."[35]

Reynolds et al. reported a series of patients in which obturator dissection was performed via a lateral groin incision over the inferior pubic ramus at the level of the obturator foramen, typically in conjunction with orthopedic surgery. All the patients in the series presented with "recalcitrant and devastating" groin pain after a transobturator sling procedure (5% to 16% of patients). According to the authors, "Groin pain after transobturator procedures is believed to be related to obturator nerve damage or entrapment and to resulting neuropathy. In addition, it may be nonneural in origin, and related to tension between the mesh material and adductor tissues." In transobturator procedures, the "trocar and mesh penetrate several muscles and structures of the inner thigh and pelvis, including (in order from external to internal) the gracilis muscle, adductor brevis muscle, obturator externus muscle, obturator membrane, obturator internus muscle and periurethral endopelvic connective tissue." Intraoperatively, the mesh was typically "closely associated to or traversing the adductor longus muscle and tendon insertion with significant fibrous reaction in all cases, and in 1 case the mesh was intimately associated with the obturator neurovascular bundle." The authors noted the dispute over the best timing for removal of a sling when pain develops postoperatively, an issue should have been resolved before marketing a device.[36]

Barber reported that the rate of requiring additional surgery for mesh complications is almost 50% in some series and seems to be higher in those undergoing partial excision at the initial operation. Recurrent pelvic organ prolapse was noted in 29% after complete excision and 5% of partial excisions. Dr. Barber described the removal of mesh for vaginal contraction, pain and dyspareunia, "If tenderness is focal and associated with a clearly defined contraction band, typically a lateral mesh arm, then transection of the contraction band without excision of the remaining mesh may provide adequate pain relief. If the tenderness is not localized or if release of the contraction band is not successful, then complete excision of the intra-vaginal portion of the mesh should be performed. This is done using the same technique as described previously for vaginal mesh exposure. The mesh arms should be transected as lateral as possible and all

contraction bands released."[37]

Blandon also detailed the challenges of removal surgery. "The vaginal surgeon is faced with the challenges of very complex surgical dissections. If mesh excision is warranted, tissue fibrosis, scarring, bleeding, and urinary tract and anorectal injury are easily encountered, which add to patient morbidity...Moreover, whereas minor complications such as small vaginal mesh erosions are simple and easy to manage, incapacitating pelvic pain, dyspareunia, and large-scale erosions can be exceedingly complex and not easily resolved."[38]

Crosby et al. at the University of Michigan, Ann Arbor, recently reported a 10-fold rise in the number of vaginal mesh removals in the past five years. The authors found that removal of vaginal mesh was helpful in relieving presenting symptoms, but complete resolution of symptoms, especially pain or dyspareunia, occurs in less than half of patients following excision.[39,40] Hartshorn also reported on mesh complications as an increasingly common indication for referral to tertiary care centers.[41] Pain resulting in deterioration of sexual function is a common symptom that is often managed by surgical removal of mesh. Based on this sample, surgical removal of mesh does not appear to improve pain related to sexual activity or overall sexual function. This has significance in the preoperative counseling of patients who are candidates for removal of transvaginal mesh.

My experience confirms the difficulty and often impossibility of removing the entire mesh product. Because of the location of mesh devices, tissue ingrowth, inflammation, and scar plate, removal surgery is often risky and complex. In most instances, remnants of mesh or mesh fibers are left behind. Multiple procedures may be required and results are often less than optimal, particularly when the mesh devices are removed for pain.

[35] Rogo-Gupta, 2013.

[36] Reynolds, W. S., Kit, L. C., Kaufman, M. R., Karram, M., Bales, G. T., & Dmochowski, R. R. (2012). Obturator foramen dissection for excision of symptomatic transobturator mesh. J Urol, 187(5), 1680-1684. doi: 10.1016/j.juro.2011.12.065

[37] Barber, M. D. (2013). Surgical techniques for removing problematic mesh. Clin Obstet Gynecol, 56(2), 289-302. doi: 10.1097/GRF.0b013e3182856371

[38] Blandon, R. E., Gebhart, J. B., Trabuco, E. C., & Klingele, C. J. (2009). Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J Pelvic Floor Dysfunct, 20(5), 523-531. doi: 10.1007/s00192-009-0818-9

[39] Crosby, E. C., Berger, M. B. DeLancey, I.L., Fenner, D.E. & Morgan, D. M. (2012). Symptom resolution after operative management of complications from vaginal mesh.

Female Pelvic Medicine & Reconstructive Surgery, 18 (5), 2

[40] Crosby, E.C., Abernethy, M., Berger, M.B., DeLancey, J.O., Fenner, D.E., Morgan, D.M. (2014). Symptom Resolution After Operative Management of Complications From Transvaginal Mesh. Obstet Gynecol, 123(1), 134-139

[41] Hartshorn, T.G., Rogo-Gupta, L., Tarvay, C.M., Rodriguez, L.V. & Raz, S. (2012). Sexual function after surgical removal of transvaginal mesh. AUGS, Poster Presentation 35.

8. A literature review of transvaginally placed surgical meshes raises serious concerns about the safety and efficacy of these products for prolapse repair.

A product may be defective if the risks do not outweigh the benefits or is "not reasonably safe." Mesh kits for pelvic organ prolapse and SUI offer no benefits over traditional repairs.

The initial studies on efficacy of POP mesh kits seemed to demonstrate an anatomic improvement in the anterior compartment. These studies can now all be discredited for various reasons. There were never any benefits identified in the apical or posterior compartment, any reduction in reoperations for recurrent prolapse, or any improvement in Quality of Life measurements. In the past couple of years, several papers have re-looked at the efficacy of native tissue repairs as compared to TVM procedures and found no improvements in efficacy.

The double-blinded randomized controlled trial initiated by Iglesia was halted because of excessive erosion, recently reported 3-year data on efficacy. Sokol and the other authors found cure rates and satisfaction after prolapse repair with and without mesh were high based on absence of prolapse beyond the hymen, lack of bulging symptoms and global impression of improvement (PGI-I).[42] This study draws into question the long-term value of vaginal mesh compared to native tissue repairs. Subjects in the mesh group suffered complications unique to vaginal mesh without long-term benefit as there was no perceived difference in success.

Stanford reviewed the literature on the success of traditional/native tissue success versus mesh-augmented repairs and found the "overall success rates of NT and MA repairs when recurrent prolapse is the primary outcome measure are very similar."[43] Oversand also found POP surgery using native tissue repair entails low reoperation rates with excellent subjective and objective results, few complications and should be the first

[42] Iglesia, C. B., Sokol, A. I., Sokol, E. R., Kudish, B. I., Gutman, R. E., Peterson, J. L., & Shott, S. (2010). Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol, 116(2 Pt 1), 293-303. doi: 10.1097/AOG.0b013e3181e7d7f8

[43] Stanford, E. J., Cassidenti, A., & Moen, M. D. (2012). Traditional native tissue versus

mesh-augmented pelvic organ prolapse repairs: providing an accurate interpretation of current literature. Int Urogynecol J, 23(1), 19-28. doi: 10.1007/s00192-011-1584

choice in treating primary POP.[44] Funk and Visco analyzed 27,809 prolapse surgeries from an insurance database. The authors "found evidence that the use of mesh for anterior vaginal wall prolapse was associated with an increased risk of any repeat surgery, which was driven by surgery for mesh removal. Vaginal mesh and native tissue repair for anterior prolapse had similar 5-year risks for recurrent prolapse."[45]

I have reviewed the reliable scientific literature regarding the use of transvaginal mesh for prolapse repair. From these studies (and confirmed by my clinical experience), I have made the following conclusions regarding the efficacy of these products:

There is no good evidence supporting benefit in quality of life (QOL) or relief of symptoms in any compartment with the use of trans-vaginal mesh for the treatment of POP. A recent study of 27,809 anterior prolapse surgeries with 49,658 person- years of follow-up determined that native tissue and vaginal mesh surgery had similar 5-year risks for surgery for recurrent prolapse.[46]

There is no reduction in reoperation rates for prolapse in any compartment with the use of trans-vaginal mesh for the treatment of pelvic organ prolapse. There is no evidence of anatomic benefit with the use of trans-vaginal mesh for the treatment of POP in the posterior or apical compartments.

There are studies that suggest anatomic benefit in the anterior compartment only, but this finding has limited, if any, clinical significance. Other studies show no anatomic benefit. Recent studies indicate that the anatomic benefits (anterior compartment only) suggested in earlier trials are unfounded and the result of bias.

The total number of reoperations is higher in mesh repairs due to the rate of surgeries for repair of complications.

I have made the following conclusions regarding the safety of these products from my review of the scientific literature:

1. Adverse events and complications are common.

2. Many of these complications do not occur with traditional prolapse repairs.

3. Many of these complications are life-altering and permanent, unlike those seen with traditional prolapse repairs.

4. Many of these complications require additional surgery, which may or may

not alleviate the symptoms - unlike traditional prolapse repairs.

[44] Oversand, S. H., Staff, A. C., Spydslaug, A. E., Svenningsen, R., & Borstad, E. (2013). Long-term follow-up after native tissue repair for pelvic organ prolapse. Int Urogynecol J. doi: 10.1007/s00192-013- 2166-z

[45] Funk, M. J., Edenfield, A. L., Pate, V. & Visco, A. G. Trends in mesh use between vaginal prolapse repair and sacrocolpopexy, 2005-2010. Female Pelvic Medicine & Reconstructive Surgery, 18 (5), 2.

[46] Funk, M. J., Levin, P. J., & Wu, J. M. (2012). Trends in the surgical management of stress urinary incontinence. Obstet Gynecol, 119(4), 845-851

5. The study noted above with 27,809 anterior prolapse surgeries with 49,658 person years of follow-up determined that the use of mesh for anterior prolapse was associated with an increased risk of any repeat surgery, which was driven by surgery for mesh removal.[47]

6. These complications can occur at any time, unlike complications occurring with traditional prolapse repairs.

7. Explant surgery, when indicated, is risky, difficult to perform, and may or may not alleviate symptoms.

I have concluded the following regarding the differences regarding the mesh complications and those associated with traditional surgery:

1. Many of the complications reported occur only with mesh. These include erosion and extrusion, mesh contraction syndrome, organ perforation from mesh, partner injury, severe vaginal pain, granulomas, and need for multiple surgical procedures for removal and attempted relief of pain.

2. Mesh complications, as opposed to complications with traditional repairs, are likely to be more frequent and more severe. Examples include dyspareunia, de novo stress urinary incontinence, chronic pelvic pain, neuromuscular injury, and emotional sequelae.

3. Most mesh complications are more difficult to treat. This includes fistulae, bleeding, infection, bowel/bladder injuries, dyspareunia, pelvic pain, and recurrent prolapse.

4. The potential for complications lasts indefinitely because the synthetic mesh is permanent.

5. Some risks are still unknown and cannot be known for many years to come.

Similar literature is available for SUI. Synthetic slings are no more effective than traditional Burch procedure or autologous slings and create unique and, sometimes severe complications.[48] For example, in a randomized controlled trial by Amaro, satisfaction

[47] Funk, 2012.

[48] Albo ME, Richter HE, Brubaker L, Norton P, Kraus S, et. al.; Burch colposuspension versus fascial sling to reduce urinary stress incontinence; New England Journal of Medicine 2007;356:2143-2155; Amaro, J. L., Yamamoto, H., Kawano, P. R., Barros, G., Gameiro, M. O. O., & Agostinho, A. D. (2009). Clinical and quality-of-life outcomes after autologous fascial sling and tension- free vaginal tape: a prospective randomized trial. Int Braz J Urol, 35:60-67; Birch, C., & Fynes, M. M. (2002). The role of synthetic and biological prostheses in reconstructive pelvic floor surgery. Curr Opin Obstet Gynecol, 14(5), 527-535; Blaivas, J. G., & Chaikin, D. C. (2011). Pubovaginal fascial sling for the treatment of all types of stress urinary incontinence: surgical technique and long-term outcome. Urol Clin North Am, 38(1), 7-15, v. doi: Blaivas, J. G., Purohit, R. S., Weinberger, J. M., Tsui, J. F., Chouhan, J., Sidhu, R., & Saleem, K. (2013). Salvage Surgery after Failed Treatment of Synthetic Mesh Sling Complications. J Urol. doi: 10.1016/j.juro.2013.03.044; Brown, S. L. & Govier, F. E. (2000). Cadaveric versus autologous fascia lata for the pubovaginal sling: surgical outcome and patient satisfaction. The Journal of Urology, 164:1633- 1637; Broussard, A. P., Reddy, T. G., Frilot II, C. F., Kubricht III, W. S., & Gomelsky, A. (2013). Long- term follow-up of porcine dermis pubovaginal slings. Int Urogynecol J, 24:583-587; Brubaker, L., Richter, H.E., Norton, P.A., Albo, M., Zyczynski, H.M., Chai, T.C., Zimmern, P., Kraus, S., Sirls, L., Kusek, J.W., Stoddard, A., Tennstedt, S., Gormley, A. (2012). 5-Year Continence Rates, Satisfaction and Adverse Events of Burch Urethropexy and Fascial Sling Surgery for Urinary Incontinence. J Urology, 187: 1324- 1330, 10.1016/j.ucl.2010.12.002

rates were 62.5 to 97.5% in AFS group, while in TVT group it was between 36 to 80%. In this study, AFS and TVT yielded similar results, except for operating time which was shorter in TVT[49]. Chapple recommended that when a patient has made the decision to proceed with surgery, alternative surgical options that include non–mesh-based techniques should be offered, such as an autologous fascial sling or bladder neck suspension.[50]

In a recent review article published in Nature, one of the most prestigious journals in the world, Blaivas described the complications associated with synthetic mesh slings. The most common risks in patients with SMUS include urethral obstruction requiring surgery (2.3% of patients with SMUS), vaginal, bladder and/ or urethral erosion requiring surgery (1.8%) and refractory chronic pain (4.1%). At least one third of patients developed recurrent SUI, based on the review. Additionally, complications are under-reported. The authors provide and excellent discussion of the mechanisms by which synthetic slings produce complications – all based on peer-reviewed, reliable medical

literature.[51]

Both the American College of Obstetrics and Gynecology and the American Urology Association endorse the use of autologous slings and Burch procedure.[52]

Recent literature is finally addressing the long-term consequences of vaginal mesh complications and the outcomes of attempts at surgical treatment - reporting large numbers of patients in academic medical centers like Emory. This reflects the lag time between the appreciation of these devastating complications for those of us in a referral practice and awareness by community physicians. These studies show a significant number of women who fail to respond to treatment despite the best care available and remain in worse condition than they were before having the initial operation.[53]

[49] Amaro, J. L., Yamamoto, H., Kawano, P. R., Barros, G., Gameiro, M. O. O., & Agostinho, A. D. (2009). Clinical and quality-of-life outcomes after autologous fascial sling and tension- free vaginal tape: a prospective randomized trial. Int Braz J Urol, 35:60-67

[50] Chapple, C. R., Raz, S., Brubaker, L., & Zimmern, P. E. (2013). Mesh Sling in an Era of Uncertainty: Lessons Learned and the Way Forward. Eur Urol. doi: 10.1016/j.eururo.2013.06.045

[51] Blaivas, et al., Safety considerations for synthetic sling surgery, Nat. Rev. Urol. advance online publication 18 August 2015; doi:10.1038/nrurol.2015.183

[52] ACOG Practice Bulletin Number 155, November 2015; Dmochowski et al. U t least one-third of patients undergoing sling excision surgery develop recurrent SUI. Update of AUA Guideline on the Surgical Management of Female Stress Urinary Incontinence J Urol ol. 183, 1906-1914, May 2010

[53] e.g. Hammett, J., et al. (2014). "Short-term surgical outcomes and characteristics of patients with mesh complications from pelvic organ prolapse and stress urinary incontinence surgery." Int Urogynecol J 25(4): 465-470; Dunn, G. E., et al. (2014). "Changed women: the long-term impact of vaginal mesh complications." Female Pelvic Med Reconstr Surg 20(3): 131-136; Hansen, B. L., et al. (2014). "Long-term follow-up of treatment for synthetic mesh complications." Female Pelvic Med Reconstr Surg 20(3): 126- 130; Abbott, S., et al. (2014). "Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study." Am J Obstet Gynecol 210(2): 163 e161-168; Unger, C. A., et al. (2014). "Outcomes following treatment for pelvic floor mesh complications." Int Urogynecol J 25(6): 745-749;

I am not aware of any other surgical procedure that has created a “new disease” such as

that we are seeing since the introduction of trans-vaginal mesh. It has even been given a name in the recent literature, "Meshology."[54]

In my opinion, the risks of polypropylene mesh in vaginal prolapse and SUI repairs outweigh the benefits.

[54] Lee et al., Meshology: a fast-growing field involving mesh and/or tape removal procedures and their outcomes, Expert Rev. Med. Devices Early online, 1–16 (2014)

IV. DISCUSSION OF FINDINGS REGARDING PLAINTIFF

Margaret Carolyn Acosta (dob [redacted])

Product: Gynemesh PS lot# BJP139 implanted 6/9/2010

Implanting surgeon Robert A. Armada, DO

Mesh Revision Surgeries:

1. 5/15/2014, San Antonio Regional Hospital, Robert Armada, DO
2. 3/10/2016, UCLA Medical Center, Shlomo Raz, MD;
3. 3/6/2017, UCLA Medical Center, Shlomo Raz, MD

Chronology of clinical records:

Margaret 'Carolyn' Acosta (dob [redacted] is a former mortgage loan officer (2005-2015) and mother of one, with a past history of appendectomy in 1979, an ectopic pregnancy in 1981, and hysterectomy in 1990. Her health challenges have included back and neck problems. In 1999, at the age of 39, lumbar spine fusion surgery was done for problems of chronic low back pain (L 4-5), and later cervical spine surgery (C 6-7) in 2001, and later revision (C 5-6) was needed in 2006.

On 6/9/2010, at age 50 years Dr Robert Armada performed a modified Marshall-Marchetti-Krantz procedure with Mitek screw fixation and both anterior and posterior repairs with Gynemesh PS for vaginal wall prolapse. The indication for surgery was "problems of urinary stress incontinence for the last 15 years but worse in the last 2 years." "The patient also complains of constant pelvic pressure." Admitting diagnoses included - rectal pain, constipation associated with rectocele, stress urinary incontinence, and a large cystocele. The post-operative course and recovery were uneventful.

Four years later, on 05/15/2014, Ms. Acosta was re- admitted for surgical revision. The chief complaint was pelvic pain and the diagnosis was vaginal mesh erosion into the vagina and rectocele. Dr Armada performed local excision of the exposed mesh on the posterior vaginal wall and posterior repair. The operative report does not define the dimensions of the vaginal mesh erosion nor the precise anatomical location. The post-operative course and recovery were uneventful.

On 10/02/2015, Ms. Acosta was admitted as an emergency to the care of Dr Arnold Roth, for problems of severe reactive airways disease and respiratory failure with hypoxemia secondary to Fentanyl patch used to treat her chronic pelvic pain secondary to pelvic mesh. The medical record reflects – "The patient has chronic pelvic pain secondary to deteriorating and probably displaced pelvic mesh for bladder suspension, placed 6 years ago. The patient has been unable to have pain control with oral medications. The patient was started on Fentanyl patch and the patient approximately a week ago had increasing cough, sputum production, dyspnea and wheeze, treated with home medication, nebulizer, Solu-Medrol, and antibiotic. The patient had significant worsening on the day prior to admission. On the morning of admission she was unable to catch her breath. The patient presented to the emergency room and had severe hypoxic episode."

The clinical diagnosis was acute respiratory failure secondary to allergic reaction with reactive airway disease, probably due to fentanyl patch narcotic analgesia used for chronic pelvic pain secondary to retained pelvic mesh.

On 02/18/2016, Ms. Acosta was admitted again as an emergency to the care of Dr Roth, after a week of increasing pelvic pain, she had gone again to the emergency room and was discharged on oral Keflex for UTI, but her course had continued worsening of pelvic/perineum pain, nausea, vomiting, fever, decreased cognitive functioning, fatigue and difficulty getting out of bed. Ms. Acosta had presented to the office appearing toxic." A diagnosis was made of bilateral cellulitis of the proximal medial thighs with perineal inflammation and infection secondary to retained bladder suspension mesh. The medical record reflects that Ms. Acosta "was admitted for fever, chills, nausea, decreased food and fluid intake." Findings included "tenderness right buttock to perineum." "The patient reported vaginal discharge with blood-tinge just prior to admission" "The patient was admitted to medical/surgery and treated with IV Zosyn and Flagyl. The patient had rapid resolution of bilateral medial thigh rash. Perineal pain persisted." "MRI was negative for fasciitis or foreign body" "The patient had severe pain". "The patient was evaluated by GYN who had placed the mesh. Treatment was unsuccessful." "The patient went to mesh retrieval specialist at USC in 10/2015. The patient was scheduled in 02/2016 for removal of mesh using special procedures." "The patient unfortunately had procedure canceled because of surgical scheduling. The patient has had worsening of perineal pain requiring bed rest for up to 1 week." Ms. Acosta was discharged from hospital on 02/24/2016 "with PICC line" for continued antibiotic therapy.

On 3/10/2016, Dr Shlomo Raz (aforementioned "mesh retrieval specialist") performed extensive vaginal surgery to remove retained polypropylene foreign material including exploration of the anterior vaginal wall for mesh erosion, excision and reconstruction of the anterior vaginal wall after removal of mesh from the bladder wall, also exploration and removal of residual posterior mesh, posterior vaginal wall reconstruction and removal of a pelvic mass adherent to the rectal wall. Ms. Acosta tolerated the procedure well and the post-operative course and recovery were at first uneventful.

On 5/10/2016, Ms. Acosta was readmitted to the care of Dr Roth for problems of persistent severe diarrhea and dehydration, fever, chills, myalgia and malaise. The medical record reflects – "patient states that 5 days ago, she had acute onset of severe abdominal pain followed by persistent watery diarrhea. The patient developed bloody mixture with the diarrhea. The patient developed nausea, vomiting." "The patient was evaluated and noted to be significantly ill and appearing toxic." The diagnosis was recurrent Clostridium difficile enterocolitis with sepsis due to antibiotic therapy - "a complication of prolonged antibiotic therapy needed to treat the cellulitis and infection problems related to retained pelvic mesh" The C. difficile infection did improve with oral Vancomycin therapy and fluid resuscitation and Ms Acosta was able to be discharged after more than one week of intensive inpatient care to continue her treatments at home.

On 9/19/2016, Dr Raz performed an autologous fascial sling procedure in an effort to address the problems of stress urinary incontinence. Fascia was harvested from the left thigh for this procedure.

On 12/28/2016, Ms Acosta was re-admitted for another episode of infection – "bronchiolitis with reactive airways disease and hypoxemia". Other diagnoses recorded at that time included chronic pelvic pain secondary to deterioration of pelvic mesh, status post removal, overactive bladder and stress urinary incontinence. The respiratory symptoms did improve with intensive therapy.

On 3/6/2017, Dr Raz performed a further procedure for more exposed mesh that had not been apparent at the time of prior surgery, six months earlier in September. The eroded mesh was found on the posterior vaginal wall just one centimeter from the posterior fourchette – that is at the opening of the vaginal hiatus and immediately adjacent to the anus.

Ms. Acosta reports that before placement of the Gynecare PS mesh her activities included - "Rode my horse on the farm, worked a lot – open houses, meeting with clients, lifting computers; could drive long distances for trips; played with my grandson; had sex with my husband; normal household activities – laundry, grocery shopping, housework, cooking". Since the mesh implant surgery and subsequent complications, Ms Acosta is "Unable to drive long distance or sit for too long due to the pain; cannot lift anything heavy; cannot do normal housework due to pain, cannot play with my grandson, no longer able to ride my horse, cannot have sex with my husband".

Margaret Carolyn Acosta has experienced mesh-related complications including chronic persistent pelvic pain requiring long-term opioid medications, mesh erosion, dyspareunia, urinary tract infections, vaginal pain, rectal pain, recurrence of incontinence, bladder and bowel dysfunction, nerve damage, and mesh extrusion leading to the need for three removal surgeries. These complications are caused primarily by the Gynemesh PS product. More likely than not, these injuries are the direct result of the defects inherent in the Gynemesh PS devices, including source of chronic inflammation, foreign body reaction, deformation, scarring and fibrosis, hardening, nerve damage, and degradation of the polypropylene mesh. These injuries were foreseeable based on experience with hernia

mesh and the use of mesh in other pelvic applications.

In addition to these well known pelvic mesh complications, Ms. Acosta has survived three distinct life-threatening illnesses related to the mesh, and indeed has been fortunate to survive thanks to the admirably prompt and aggressive medical attention by Dr Roth and his team.

The first episode was in October of 2015, when Ms. Acosta was admitted as an emergency for severe reactive airways disease and respiratory failure secondary to narcotic medication (Fentanyl) used to treat her chronic pelvic pain secondary to pelvic mesh. The second was in February of 2016, admitted as an emergency this time for cellulitis and septicemia. The source of sepsis was "secondary to retained bladder suspension mesh" as documented in the medical record. The final life-threatening event was in May 2016, when Ms. Acosta was admitted for recurrent Clostridium difficile enterocolitis with sepsis - "a complication of prolonged antibiotic therapy needed to treat the cellulitis and infection problems related to retained pelvic mesh". It should be noted that the mortality rate for recurrent C difficile infections is up to 30%. [Kelly CP, LaMont JT, Clostridium difficile – more difficult than ever. N Engl J Med. 2008;359:1932-40. DOI PubMed]

The physicians who treated Ms. Acosta including Dr. Armada and Dr. Raz met the standard of care. Specifically, the implant operative note does not reveal any errors in surgical technique. In my experience, and supported in the medical literature, the "piecemeal" local excision of exposed mesh does not produce optimal outcomes. However, this is a common practice among physicians and Ethicon did not provide guidance on the management of complications for doctors using their products. There were safer alternatives, including paravaginal repair, colpopexy, native tissue repairs, or autologous fascial lata that would have avoided the injuries experienced by Ms. Acosta. An abdominal POP repair using a lighter weight larger pore mesh as opposed to the transvaginal repair using the Gynemesh PS would have significantly reduced or eliminated the injuries experienced by Ms. Acosta.

I performed a differential diagnosis to reach these conclusions. I considered and factored in all the information contained with the materials reviewed into my differential diagnosis considering alternative causes and ruling them out as the cause of her symptoms. Exposure of mesh and erosion of mesh are unique complications of mesh. Ms. Acosta did not have any significant pelvic pain issues prior to implantation of the vaginal Gynemesh PS product. The medical record reflects that prior to the mesh implantation she had no difficulties with intercourse.

Her hysterectomy did not contribute to the complications. She is menopausal and, like all women who are menopausal, has some degree of vaginal atrophy. Vaginal atrophy does not produce focal pain, vaginal induration or other findings and is treatable with local estrogen. Other personal medical history including one vaginal delivery, lumbar spine and cervical spine problems, and Ms. Acosta's remote history of appendectomy and ectopic pregnancy do not explain the clinical course. Likewise, these are not the cause of her persistent chronic pelvic pain requiring daily narcotic analgesics nor the persistent

vaginal symptoms and exam findings. The prior history of back and neck problems may contribute to bladder and bowel symptoms, but fail to explain the clinical course of events.

I reviewed the IFU for the Gynemesh PS device. In no way, does the IFU describe the injuries experienced by Ms. Acosta. The IFU does not provide information regarding the frequency, severity, lack of responsiveness to treatment, and permanence of complications associated with the product. It provides no guidance to doctors on ways to manage these complications. The IFU misrepresents the material properties of polypropylene by describing "a minimum to slight inflammatory response, which is transient", a "deposition of a thin fibrous layer of tissue", and "soft and pliable". The IFU also states that the mesh is not "subject to degradation or weakening by the action of tissue enzymes." The peer-reviewed scientific and medical literature clearly contradicts these statements.

The IFU incorrectly states that a "transitory local irritation at the wound site and a transitory foreign body reaction may occur". The IFU also misrepresents the life changing and unique complications associated with trans-vaginally placed mesh devices by stating, "potential adverse reactions are those typically associated with surgically implantable materials". This is inconsistent with the medical literature and my clinical experience.

The IFU does not address the potential for ongoing adverse events. It does not address the recalcitrant and recurrent nature of many vaginal mesh exposures and erosions suffered by Ms. Acosta. The IFU does not address the risk of permanent vaginal scarring and distortion, chronic pain, sexual impairment, and dyspareunia. The IFU does not inform physicians of the difficulty and risks involved in removing these devices, the need for multiple surgeries, or the failure of surgery to correct the problems in many cases.

Dr Armada, the implanting surgeon was aware of the initial complication of pelvic pain, recognized the vaginal mesh erosion and performed local excision of the exposed mesh, but was ill equipped when further complications occurred with bilateral cellulitis and perineal inflammation and infection secondary to retained bladder suspension mesh. Ms. Acosta was "evaluated by GYN who had placed the mesh", but "Treatment was unsuccessful." The implanting surgeon had not been trained to manage the complications of Gynemesh PS, instead Ms. Acosta had to seek help from a "mesh retrieval specialist at USC" – "for removal of mesh using special procedures." A further deficiency of Gynemesh PS design was that in spite of Ms. Acosta's severe complications, modern imaging techniques including magnetic resonance imaging studies were unable to detect the presence of mesh. (MRI 02/19/2016)

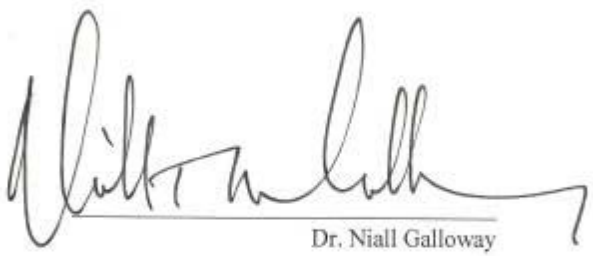
This case reflects a very common feature of mesh complications, that problems typically occur years after implantation; the medical literature is burgeoning with reports of single center series with only short term follow up and these "research studies" by definition are blind to late and long-term patterns of complication. This may help to explain why the private practitioners have been so much slower than academic pelvic surgeons to recognize the inherent dangers of vaginal mesh design.

Ms. Acosta's prognosis is guarded due to the chronicity of her symptoms and the persistence of her chronic vaginal and pelvic pain. She might still have remaining residual mesh fragments - in spite of three surgical procedures to remove the mesh - and it is likely that she will require additional medical, and possibly surgical treatment to address her ongoing chronic pelvic pain and other symptoms, including dyspareunia, urinary tract infections, vaginal pain, rectal pain, bladder and bowel problems, recurrence of incontinence and nerve damage.

In my opinion, the Ethicon's Gynemesh PS Prolene product used in Ms. Acosta was unreasonably dangerous because the risks far outweighed the benefits, Ethicon did not warn doctors and patients of the serious risks, and Ethicon made inaccurate and misleading representations as to its safety. It was unreasonably dangerous because Ethicon did not provide Ms. Acosta or her doctors with accurate and complete information and warnings. Finally, claims made by Ethicon regarding the product's performance that were known to be misleading or untrue make the product unreasonably dangerous.

I reserve the right to supplement my opinion regarding her injuries and reasonable necessity of future care as her prognosis develops.

Signed this 19th day of August, 2019



Dr. Niall Galloway